REMARKS

Upon entry of the foregoing amendment, claims 1- 10 will remain pending in the application. Claims 1-7 and 10 have been amended. These changes do not introduce new matter, and their entry is respectfully requested.

In the Office Action of March 17, 2008, the Examiner set forth a number of grounds for rejection. These grounds are addressed individually and in detail below.

In the Specification

The Specification is objected to for lack of a brief description of drawings. A Brief Description of the Drawings has been added to page 3 of the specification. Applicants respectfully submit that the ground of the objection has been obviated. Withdrawal of the objection to the specification is respectfully requested.

Claim Rejections Under 35 U.S.C. § 112

Claims 1-7 and 10 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for the reasons set forth on 2-3 of the Office Action. Specifically, the Examiner alleges that the phrase "essentially consisting of" in claim 1 is not a synonym for the transitional phrase "consisting essentially of," and that claim 3 recites "preferred" enzymes which do not precisely define the metes and bounds of the claim.

Claim 1 has been amended to replace the phrase "essentially consisting of" with the transitional phrase "consisting essentially of." Claim 3 has been amended to delete the recitation of "preferred" enzymes. Applicants respectfully submit that the amendments obviate the grounds of the rejection. Withdrawal of the rejection under 35 U.S.C. 112, second paragraph, is respectfully requested.

Claim Rejections Under 35 U.S.C. § 103

Claims 1-5, 7 and 10 stand rejected under 35 U.S.C. §103(a) over Leskovar et al. (hereinafter "Leskovar") (WO 89/09620) for the reasons set forth on pages 3-8 of the Office Action. Claims 1-7 and 10 stand rejected under 35 USC 103(a) over Leskovar in view of Housman et al. (hereinafter "Housman") (US 6,200,754) for the reasons set forth on pages 8-9 of the Office Action. Applicants respectfully traverse the rejections.

To establish a *prima facie* case of obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970).

Independent claim 1 of the instant application is directed to a pharmaceutical composition for cancer therapy consisting essentially of: a) at least one compound having glutaminase activity; b) at least one antineoplastic agent selected from the group consisting of platinum complexes and anthracyclines; and c) at least one of carrier substances, auxiliary substances, and pharmaceutical injection media.

In contrast, Leskovar generally describes a medicament which comprises (1) antibodies or conjugates of antibodies and cytotoxic agents *(i.e.*, component A) and (2) activators of effector cells (*i.e.*, component B). The cytotoxic agents include anthracyclines such as doxorubicin and daunomycin (Leskovar, paragraph [0023]). The conjugates of antibodies include antibodies conjugated to asparaginase or glutaminase (Leskovar, paragraph [0192]).

Leskovar, however, does not teach or suggest a pharmaceutical composition that does not contain activators of effector cells, as implied by the transitional "consisting essentially of" in instant claim 1. In fact, by including activators of effector cells as one of the two key ingredients of the claimed invention, Leskovar **teaches away** from a composition that does not contain activators of effector cells. For this reason alone, claim 1 is patentable over Leskovar.

Moreover, Leskovar fails to teach or suggest using unconjugated anthracyclines in a pharmaceutical composition, as recited in the instant claim 1. The Examiner alleges that "the broad term of antineoplastic agent consisting of platinum complexes and anthracyclines reads on any compound that incorporates these, including immunoconjugates" (Office Action, page 4). Applicants respectfully disagree.

The claim language makes it clear that the term "anthracylines" is part of a Markush group. Therefore, an antineoplastic agent can be a platinum complex or an anthracycline. The term "anthracycline" has a well-defined meaning in the art. Anthracycline is a member of a family of chemotherapy drugs that are also antibiotics. The anthracyclines include daunorubicin (Cerubidine), doxorubicin (Adriamycin, Rubex), epirubicin (Ellence, Pharmorubicin), and idarubicin (Idamycin). A person of ordinary skill in the art would not consider

immunoconjugates as a form of anthracycline. Therefore, the antineoplastic agent of instant claim 1 would not read upon an immunoconjugate of anthracycline.

With regard to the Examiner's opinion that a surprising effect has only been shown for a combination of Pseudomonas 7A glutaminase-asparaginase and not for any compound having glutaminase activity, we would like to direct the Examiner's attention to the assumed mechanism on page 5, last paragraph *et seq*., which discloses that cleaving of glutamine results in deprivation of energy for the cancer cells and, thus, makes the cancer cells more vulnerable. This general mechanism has been proven by using the specific example of Pseudomonas 7A glutaminase-asparaginase compound. A person of ordinary skill in the art would understand that this effect can be obtained by any compound having glutamine-cleaving activity, *i.e*., glutaminase activity.

Leskovar also fails to teach or suggest "at least one compound having glutaminase activity," as recited in instant claim 1. Although Leskovar describes an immunoconjugate of an antibody and a glutaminase enzyme, the immunoconjugate does not necessarily have glutaminase activity. It is known that coupling of the enzyme glutaminase with other molecules, *e.g*., PEG, leads to a loss of enzyme activity. In particular, the linkage of a glutaminase enzyme with the antibody changes the three-dimensional structure of the enzyme and renders the enzyme to lose its enzyme activity. Moreover, the quaternary structure of the enzyme glutaminase is changed as a result of coupling to other molecules. Glutaminase is active only in its tetrameric form (homotetramer). According to Leskovar, in order to ensure localization at the target cell, each monomer has to be modified with at least one antibody. The molecular weight of a glutaminase monomer is about 35 kDa, the molecular weight of an antibody is between about 50

and 200 kDa, depending on the Ig type. Therefore, the coupling of antibodies to a glutaminase tetramer would increase the molecular weight of the tetramer by 150% to 600%. Such a modification is likely to induce fundamental changes in the tetramer structure and the activity of the enzyme is no longer guaranteed. Accordingly, Leskovar does not disclose the use of a compound having glutaminase activity.

In addition, Leskovar does not mention using both anthracyclines and glutaminase in the same composition. The Examiner alleges that Leskovar teaches (1) Component A which includes antibody-conjugated anthracyclines (paragraphs 21-23) and (2) antibody conjugates of xenogeneic proteins can be admixed with Component A (paragraphs 25-26). The Examiner thus concluded that Leskovar teaches a composition with active substances such as enzymes and anthracyclines (page 6, 2nd paragraph of the Office Action). Applicants respectfully disagree.

Paragraph [0026] of Leskovar notes that "conjugates, composed of xenogeneous proteins, especially immunoglobulines and cytotoxins, combined with conjugates, based on the same xenogeneicd proteins and tolerogens (D-GL), can be admixed to the component A." Paragraph [0026] does not mention anything about antibody-glutaminase immunoconjugates. There is also no hint in Leskovar that the antibody-glutaminase described therein is a xenogeneous or cytotoxic protein. Accordingly, a person of ordinary skill in the art would not have been guided by Leskovar to a composition consisting of antibody-anthracycline conjugate and antibody-glutaminase conjugate, let alone to a composition consisting of anthracycline and glutaminase, as recited in claim 1 of the instant application.

Housman does not cure the deficiency of Leskovar. Housman is cited for its teachings on mitomycin C and cis-platinum. Housman does not teach or suggest a composition consisting essentially of a compound having glutaminase activity and an antineoplastic agent, as recited in claim 1.

Accordingly, Applicants respectfully submit that Leskovar and Housman, individually or in combination, do not render claim 1 obvious because they fail to teach or suggest all the claim limitations. Applicants further submit that claims 2-7 and 10 are patentable over Leskovar and Housman because they depend from claim 1 and recite additional patentable subject matter.

In view of the foregoing, Applicants respectfully submit that these grounds of rejection have been obviated and withdrawal of the rejection under 35 U.S.C. §103 is respectfully requested.

CONCLUSION

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. It is believed that a full and complete response has been made to the outstanding Office Action and, as such, the present application is in condition for allowance.

If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to contact Applicants' counsel, Ping Wang, M.D. (Reg. No. 48,328), at 202.842.0217.

Respectfully submitted,

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